



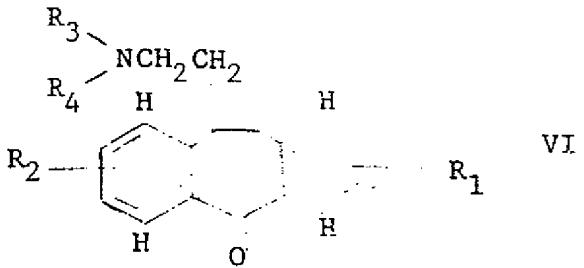
(11) AU-B1-18586/76

(12) PATENT SPECIFICATION
ABRIDGEMENT
(19) AU

(21) 18586/76 503,490 (22) 12.10.76
(23) 12.10.76 (24) 7.2.72
(43) 23.12.76 (44) 6.9.79
(51)² C07C 97/10 C07C 101/42.
(54) AMINOALKYL-DIBENZOCYCLOHEPTEN-5-ONE DERIVATIVES.
(62) 51834/72.
(71) SANDOZ PATENTS LIMITED.
(72) HOULIHAN, W.J., NADELSON, J.
(74) DM
(56) 55766/73 485383 09.66-1 09.65-4 87.19 09.62-20
09.61-2
51834/73 477574 09.66-1 09.65-4 87.19 09.61-2
09.66-7 09.66-991

(57) Compounds of formula VI as defined in claim 1 are also claimed.

CLAIM 1. A process for the production of a compound of formula VI,



in which R₁ signifies hydrogen, alkyl or alkoxy of 1 to 3 carbon atoms or fluorine,

R₂ signifies hydrogen, alkyl or alkoxy of 1 to 3 carbon atoms, fluorine or trifluoromethyl, and

R₃ and R₄ independently signify alkyl of 1 to 3 carbon atoms,

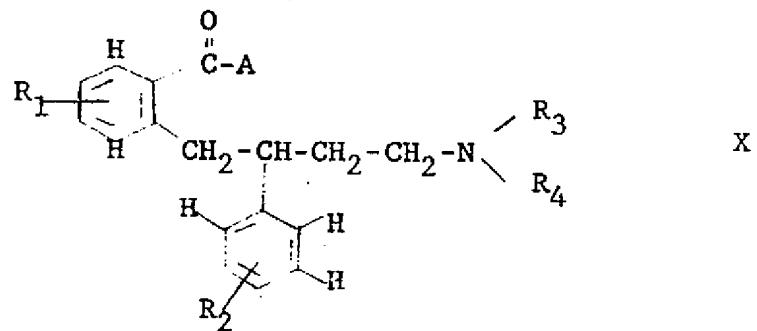
comprising cyclising, in the presence of a Lewis acid, a compound of formula X,

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ND

33.2



in which R₁ to R₄ are as defined above, and

A signifies hydroxyl, straight chain alkoxy of 1 to 4 carbon atoms or chlorine.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1973

APPLICATION FOR A PATENT

18,586/76 **503,490**

+

We SANDOZ PATENTS LIMITED, 789 Don Mills Road,
Don Mills, Prov. Ontario, Canada

hereby apply for the grant of a Patent for an invention entitled:

"AMINOALKYL-DIBENZOCYCLOHEPTEN-5-ONE DERIVATIVES"

which is described in the accompanying ~~provisional~~ complete specification.
This application is a separate application made by virtue of sub-section (1) of Section 49A of the Patents Act 1952 in respect of an invention disclosed in the complete specification lodged in respect of Australian Application No. 51834/73.
~~The application is a convention application and is based on the application(s) for patent or similar protection made~~

in

on

in

and

under No.

under No.

APPLICATION ACCEPTED AND ALLOWED
11/11/79

DATED this 8 day of November 1977

H. V. Dimington

(a member of the firm of DAVIES & COLLISON)
for and on behalf of the applicant



TO: The Commissioner of Patents
WODEN ACT 2606

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1969

DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A
18,586 /76 PATENT OR PATENT OF ADDITION

(The declaration shall be made by the applicant, or, if the applicant is a body corporate, by a person authorized by the body corporate to make the declaration on its behalf).

In support of the Application made for a patent
of addition for an invention entitled"AMINOALKYL-DIBENZOCYCLOHEPTEN-5-ONE
DERIVATIVES"

Insert title of invention.

Insert full name(s) and address(es)
of declarant(s).We, Jean Kramer and Hans Rudolf Haus, both
of Sandoz Patents Limited a Canadian Body Corporate
of 789 Don Mills Road, Don Mills, Prov., Ontario
Canada,

do solemnly and sincerely declare as follows:-

1. (a) I am the applicant..... for the patent
We are authorized by patent of addition
or (b) I am authorized by

SANDOZ PATENTS LIMITED

the applicant..... for the patent
of addition to make this declaration on its behalf.

2. (a) I am the actual inventor..... of the invention

or (b) William J. Houlihan, 15 Raynold Road, Mountain
Lakes, New Jersey, United States of America, Jeffrey
Nadelson, 194 Elmwood Road, Lake Parsippany, New Jersey,
United States of Americais the actual inventor..... of the invention and the facts upon which the applicant.....
are entitled to make the application are as follows:-The inventors have assigned the invention to
the said applicantState number in which applicant(s)
derives from actual inventor(s).Insert country and date of filing
of application on which priority
is based.Insert full name of applicant in
each basic application.

(Paragraphs 3 and 4 apply only to Convention applications).

3. The basic application..... as defined by Section 141 of the Act was made
in..... on the.....
by.....
in..... on the.....
by.....

15 NOV 1976

PATENT OFFICE

4. The basic application..... referred to in paragraph 3 of this Declaration was
the first application..... made in a Convention country in respect of the invention the subject
of the application.

Declared at BASLE this 20 day of October 1976.

SANDOZ Patents Limited

Jean Kramer Hans

Note: Initial all Alterations.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1969

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE :

503,490

Class

Int. Class

Application Number :

Lodged :

This specification is filed under the
Patents Act 1952, and is entitled

Complete Specification Lodged

Accepted :

Published :

and is correct for printing.

22 AUG 1979

Priority :

Related Art :

18,586/76

Name of Applicant : SANDOZ PATENTS LIMITED

Address of Applicant : 789 Don Mills Road, Don Mills
Ontario, CanadaActual Inventor(s) : WILLIAM J. HOULIHAN
JEFFREY NADELSONAddress for Service : DAVIES & COLLISON, Patent Attorneys,
1 Little Collins Street, Melbourne, 3000

Complete Specification for the invention entitled

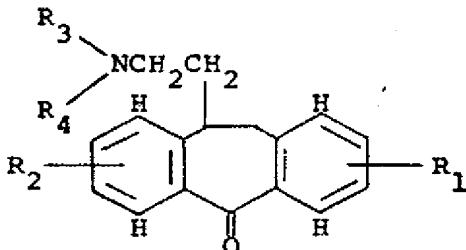
"AMINOALKYL-DIBENZOCYCLOHEPTEN-5-ONE DERIVATIVES"

The following statement is a full description of this invention, including the best method of performing it known to :—

This invention relates to aminoalkyl-dibenzo-cyclohepten-5-one derivatives.

More particularly, this invention provides
5 compounds of formula VI,

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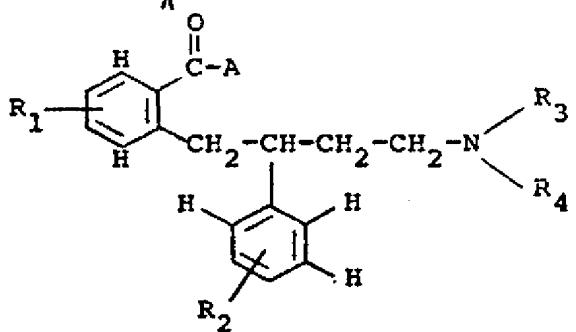
VI

in which R₁ signifies hydrogen, alkyl or
alkoxy of 1 to 3 carbon atoms or
fluorine,

R₂ signifies hydrogen, alkyl or
alkoxy of 1 to 3 carbon atoms,
fluorine or trifluoromethyl, and
R₃ and R₄ independently signify
alkyl of 1 to 3 carbon atoms.

The invention also provides a process for the

15 production of a compound of formula VI, which comprises
in the presence of a Lewis acid,
cyclising a compound of formula X,



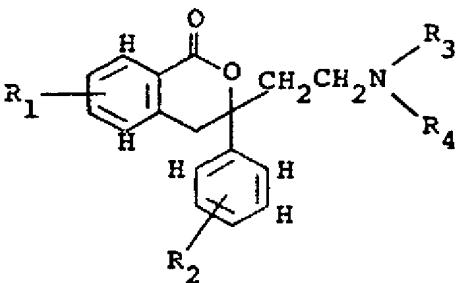
X

in which R_1 to R_4 are as defined above, and

A signifies hydroxy, straight chain alkoxy
of 1 to 4 carbon atoms or chlorine.

When A signifies hydroxyl or alkoxy, the cyclisation
is preferably effected using a strong Lewis acid such
as stannic tetrachloride, ferric chloride or titanium
tetrachloride. It is preferred to carry out the reaction
in the presence of an inert organic solvent such as
dichloromethane, carbon tetrachloride, carbon disulphide
or nitrobenzene. When A signifies chlorine, the
reaction is effected using a strong Lewis acid, preferably
in the presence of a solvent, as mentioned above. Suitable
reaction conditions generally are from 20 to 150°C,
preferably from 100 to 120°C. Reaction times are generally
about 2 to 10 hours, and under preferred conditions are
about 3 to 5 hours.

Compounds of formula X in which A signifies hydroxyl
may be prepared by reducing a compound of formula XI,



XI

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in which R₁ to R₄ are as defined above.

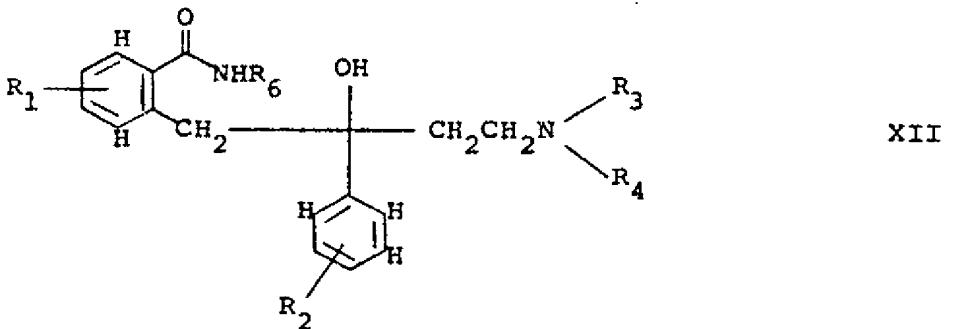
Reduction methods particularly suitable are hydrogenation in the presence of a noble metal catalyst in the presence of an inert solvent and reduction by a zinc-ammonium hydroxide system. In the hydrogenation reaction, suitable catalysts are palladium, platinum and rhodium, and these may be neat or on a support such as charcoal. Suitable solvents are alkanols of 1 to 4 carbon atoms, such as ethanol, or acetic acid.

Hydrogen pressures are conveniently about 35 to 100 psi, preferably 50 to 55 psi, and reaction temperatures are conveniently from 20 to 80°C, preferably 25 to 35°C. It is preferred to carry out the reaction in the presence of a catalytic amount of an aqueous mineral acid such as hydrochloric, sulphuric or perchloric acid. It is preferred to stop the reaction after absorption of one equivalent of hydrogen. The reduction using zinc-ammonium hydroxide is suitably carried out in the presence of a

catalyst such as cupric sulphate, and is preferably carried out in the presence of an inert organic solvent such as a lower alkanol, e.g. methanol or, especially, ethanol. Suitable reaction temperatures are from 60 to 5 100°C, preferably 75 to 85°C. Reaction times are 5 6/76 generally from about 24 to 48 hours, under preferred 6 18,588 conditions 28 to 30 hours.

11 The compounds of formula X in which A signifies chlorine or alkoxy may be prepared from 10 the acids in conventional manner.

12 The compounds of formula XI may be prepared by cyclising a compound of formula XII,

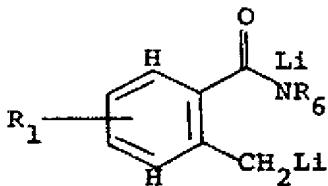


13 in which R₁ to R₄ are as defined above, and R₆ signifies alkyl of 1 to 4 carbon atoms.

14 The cyclization is preferably effected by heating the compound of formula XII, conveniently at about 60 to 220°C, preferably at 140 to 160°C, for

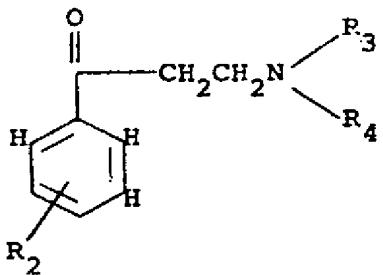
about 15 to 48 hours, under preferred conditions 20 to 28 hours. The compound of formula XII may be heated in an inert organic solvent such as tetrahydrofuran, or a hydrocarbon or halogenated hydrocarbon such as hexane, 5 heptane, benzene, toluene or o-dichlorobenzene. It is preferred to heat the compound of formula XII under an inert atmosphere, e.g. under nitrogen.

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11
The compounds of formula XII may be prepared by reacting a compound of formula XIII,



XIII

10 in which R₁ and R₆ are as defined above, with a compound of formula XIV,



XIV

in which R_2 , R_3 and R_4 are as defined above, in an inert organic solvent and under an inert atmosphere, followed by hydrolysis of the reaction product in conventional manner.

5

Suitable solvents include diethyl ether, tetrahydrofuran, hexane, heptane, benzene and mixtures thereof. The reaction is conveniently effected under nitrogen, suitably at a temperature from -30 to -15°C, preferably -25 to -20°C. Reaction times are generally 10 about 1 to 3 hours. The compound of formula XIV is preferably added in solution in the inert organic solvent to a cold (-30 to -15°C) inert organic solvent solution of the compound of formula XIII. The hydrolysis is preferably effected with aqueous ammonium chloride 15 solution in conventional manner, preferably at a temperature of from -15 to -5°C.

20

The compounds of formula X exist in acid addition salt form and may be prepared from the corresponding free bases and vice versa in conventional manner, and may be used in salt form in the reaction described hereinbefore.

The compounds of formulae X, XI and XII may be isolated and purified using conventional techniques such as crystallisation, evaporation or filtration.

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Certain of the compounds of formulae XIII and XIV are known and may be prepared by methods described in the literature, and those compounds whose preparation is not specifically described may be prepared by known methods or methods analogous to known methods from known starting materials.

A preferred group of the compounds of formula VI is that in which R_1 and R_2 , which may be the same or different, each signifies hydrogen or fluorine, and R_3 and R_4 , which may be the same or different, each signifies methyl or ethyl.

As will be appreciated by one skilled in the art, by virtue of the carbonyl group present in the compounds of formula VI, these compounds may be used to prepare a wide variety of compounds, for example a number of the compounds of formula I, as described in patent specification no. 477,574. ~~our copending Application No. 51834/73.~~

The following Example illustrates the invention.

EXAMPLE: 10-(2-Dimethylaminoethyl)-10,11-dihydro-5H-
dibenzo[a,d]cyclohepten-5-one hydrochloride

a) 2-(β-[2-Dimethylaminoethyl]phenethyl)benzoic acid
hydrochloride (compound of formula X)

5 A solution of 14.75 g (0.05 mole) of 3-(2-dimethylaminoethyl)-3,4-dihydro-3-phenylisocoumarin in 150 ml ethanol containing 1 g 10% palladium on charcoal is hydrogenated at 50 psi and room temperature until one equivalent of hydrogen is absorbed. The mixture is 10 filtered and evaporated to give the intermediate 2-[2-dimethylaminoethyl]phenethyl) benzoic acid hydrochloride form, m.p. 152° to 154°C.

b) 10-(2-Dimethylaminoethyl)-10,11-dihydro-5H-dibenzo
[a,d]cyclohepten-5-one hydrochloride (compound of
formula VI)

15 A mixture of 14.75 g (0.05 mole) of 2-(β-[2-dimethylaminoethyl]phenethyl)benzoic acid hydrochloride and 150 g of polyphosphoric acid is heated at 110°C for 6 hours, allowed to cool and poured on to crushed ice 20 with stirring. The resulting solution is cooled on ice and made basic by the addition of solid potassium hydroxide, and extracted with methylene chloride. The methylene chloride is washed with water, dried over anhydrous magnesium sulfate and evaporated in vacuo.

The residue is dissolved in isopropanol, and treated with gaseous hydrogen chloride. The resulting precipitate is filtered and recrystallized from isopropanol to give the compound 10-(2-dimethylaminoethyl)-10,11-dihydro-

5 5H-dibenzo[a,d]cyclohepten-5-one hydrochloride, m.p.

6 188-190°C.

7 Following the above procedure and using an
8 equivalent amount of ferric chloride in place of
9 polyphosphoric acid, there is obtained the identical
10 product.

11 Similarly using ferric chloride and 2-(β -[2-dimethylaminoethyl]-phenethyl)benzoic acid chloride in place of 2-(β -[2-dimethylaminoethyl]phenethyl)benzoic acid hydrochloride, the identical product is again

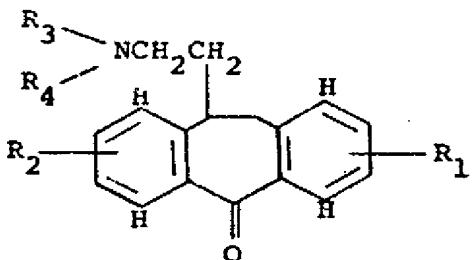
12 obtained.

13 Following the above detailed procedure but
14 using 16.3 g of 2-(β -[2-dimethylaminoethyl]phenethyl)
15 benzoic acid ethyl ester in place of 14.75 g of 2-(β -
16 [2-dimethylaminoethyl]phenethyl)benzoic acid hydro-
17 chloride, there is again obtained the identical product.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:--
~~WHATSOEVER~~

1. A process for the production of a compound of formula VI,

18,586/76



VI

in which R_1 signifies hydrogen, alkyl or
alkoxy of 1 to 3 carbon atoms or
fluorine,

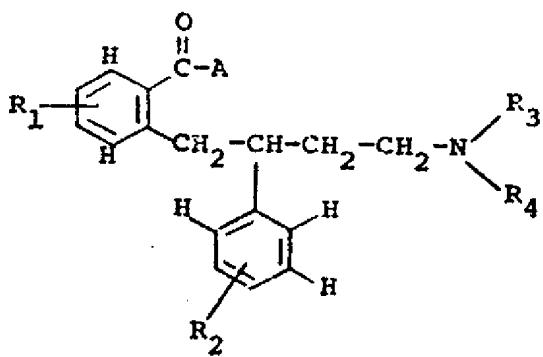
R_2 signifies hydrogen, alkyl or
alkoxy of 1 to 3 carbon atoms,
fluorine or trifluoromethyl, and

R_3 and R_4 independently signify alkyl of 1 to 3 carbon atoms.

5

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comprising cyclising, in the presence of a Lewis acid, a compound of formula X,



11

in which R_1 to R_4 are as defined above, and

A signifies hydroxyl, straight chain
alkoxy of 1 to 4 carbon atoms or
chlorine.

5 2. A process according to Claim 1, in which

10 6/76 the cyclisation is effected in the presence of an inert
6/80 organic solvent.

5/88 3. A process according to Claim 1 or 2, in
80/89 which the reaction is effected at a temperature of

10 from 20 to 150°C.

- 4. A process according to Claim 1, substantially
as hereinbefore described with reference to the Example.

5. A compound of formula VI, stated in Claim 1,
whenever produced by a process according to any
15 preceding claim.

6. A compound of formula VI, stated in Claim 1.

7. A compound of formula VI, stated in Claim 1,
in which R_1 and R_2 , which may be the same or different,
each signifies hydrogen or fluorine, and R_3 and R_4 ,
20 which may be the same or different, each signifies
methyl or ethyl.

8. 10-(2-Dimethylaminoethyl)-10,11-dihydro-5H-
dibenzo[a,d]cyclohepten-5-one.

DATED this 11 day of October 1976.

DAVIES & COLLISON

Patent Attorneys for

SANDOZ PATENTS LIMITED